

## Psychosocial Stress and Psychosis. A Review of the Neurobiological Mechanisms and the Evidence for Gene-Stress Interaction

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**This article presents evidence suggesting that psychosocial stress may increase risk for psychosis, especially in the case of cumulative exposure. A heuristically useful framework to study the underlying mechanisms is the concept of “behavioral sensitization” that stipulates that exposure to psychosocial stress—such as life events, childhood trauma, or discriminatory experiences—may progressively increase the behavioral and biological response to subsequent exposures. The neurobiological substrate of sensitization may involve dysregulation of the hypothalamus-pituitary-adrenal axis, contributing to a hypothesized final common pathway of dopamine sensitization in mesolimbic areas and increased stress-induced striatal dopamine release. It is argued that, in order to reconcile genetic and environmental influences on the development of psychosis, gene-environment interactions may be an important mechanism in explaining between-subject differences in risk following (cumulative) exposure to psychosocial stress. To date, most studies suggestive of gene-stress interaction have used proxy measures for genetic vulnerability such as a family history of psychosis; studies investigating interactions between molecular genetic measures and psychosocial stressors are still relatively scarce. Preliminary evidence suggests that polymorphisms within the catechol-*O*-methyltransferase and brain-derived neurotrophic factor genes may interact with psychosocial stress in the development of psychosis; however, extensive further investigations are required to confirm this.**

*Key words:* schizophrenia/sensitization/ethnicity/trauma/urbanicity/cannabis/gene-environment interaction

### Introduction

There is compelling epidemiological evidence that psychosocial stress is implicated in the development of psychotic symptoms. Two studies from the British National Psychiatric Morbidity Survey reported that adverse life events during the preceding 6 months were associated with psychotic experiences in a sample of the general population, both cross-sectionally and longitudinally.<sup>1,2</sup> Furthermore, a lifetime experience of upsetting life events was associated with increased levels of psychotic symptoms in individuals at high risk for schizophrenia,<sup>3</sup> although this was not confirmed in a second study in individuals at elevated risk for schizophrenia.<sup>4</sup> Rather than the impact of a single recent life event, cumulative exposure to traumatic life events may increase risk of psychosis. For example, a recent study suggested that risk for psychosis increases with the number of life events experienced.<sup>5</sup>

Other environmental factors, which could be proxies for social stress, have also been implicated. It is well established, eg, that growing up in an urban environment increases the risk for developing psychosis.<sup>6–8</sup> A study in 5618 persons from the general population found that level of urbanicity was associated with clinical and subclinical psychotic symptomatology,<sup>6</sup> a finding that was replicated in a sample of over 1 million persons from the Danish general population showing a main effect of urban birth on the development of later schizophrenia.<sup>8</sup> Another factor that has been shown to increase the risk for psychosis is migration.<sup>9</sup> The risk associated with migration may be particularly elevated in second-generation migrants, migrants from developing countries, and migrants from countries with a predominantly black population.<sup>9</sup> It has been shown that the association between migrant status and psychosis is not solely due to selection (selective migration of individuals at risk for psychosis),<sup>9</sup> and epidemiological evidence suggests that discrimination associated with migration may be involved in the risk mechanism because the degree of discrimination

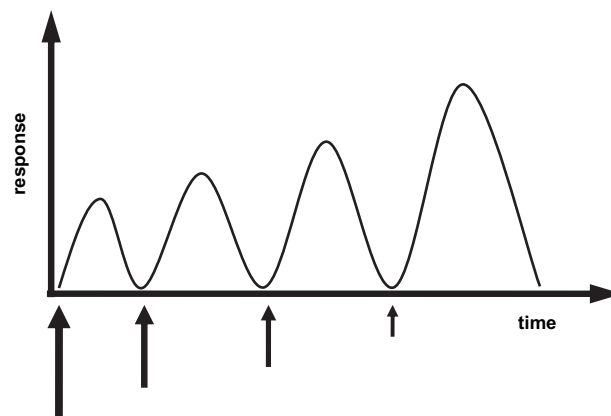
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for ethnicity was found to be associated with the relative risk for psychosis.<sup>10</sup> Furthermore, discrimination on the basis of other factors such as age, sex, appearance, sexual orientation, or handicap has been shown to similarly increase delusional ideation.<sup>11</sup> Childhood trauma has also been proposed to impact on the risk for psychosis,<sup>12</sup> although a recent systematic review of studies examining the association between childhood trauma and psychosis concluded that methodological flaws in the available studies limited the conclusions that could be drawn with regard to this putative association.<sup>13</sup>

Social defeat, defined as a subordinate position or “outsider status,” has recently been postulated as the underlying mechanism linking psychosocial aversive events to risk for psychosis.<sup>14,15</sup> An important aspect of the social defeat hypothesis is that it is a subjective phenomenon, ie, “defeat is in the eye of the beholder.”<sup>15</sup> A study examining patients with psychotic illness of recent onset found that experiencing a stressful life event increased the risk for psychotic and depressive symptom exacerbations.<sup>16</sup> However, patients did not experience more life events than controls but rather experienced them as less controllable.<sup>17</sup> These results support the vulnerability-stress model, which states that symptoms emerge whenever a threshold of stressors exceeds an individual’s vulnerability level. An individual’s vulnerability level is conceptualized as a stable within-person characteristic and aligns with other concepts such as “trait reactivity”<sup>18</sup> and “stress reactivity.”<sup>19</sup>

### *Stress Reactivity in Psychosis*

Using the experience sampling method (ESM), a structured diary technique assessing current context, mood, and psychotic symptoms in daily life (I.M.-G., M. Oorschot, D. Collip, J. Lataster, P. Delespaul, J. Van Os, unpublished data),<sup>20</sup> it was shown that increased risk for psychosis is associated with increased emotional reactivity to the small stresses of daily life. Thus, in a sample of psychotic patients in state of remission, first-degree relatives of patients with psychosis and healthy controls, patients reported a greater decrease in positive affect and a greater increase in negative affect than the healthy controls when they encountered stress, with the first-degree relatives displaying intermediate scores.<sup>19</sup> In a general population twin sample, increased psychometric risk for psychosis (ie, high scores on a schizotypy questionnaire) was associated with increased emotional reactivity to stress. Furthermore, a cross-trait cross-twin association between stress reactivity and subclinical psychosis was found, indicating that emotional reactivity to stress may be an unconfounded intermediate phenotype associated with genetic risk for psychosis (T. Lataster, M. Wichers, N. Jacobs, et al, unpublished data). Stress also increased the intensity of subtle psychosis-like symptoms in the realm of daily life, both in patients and their first-degree relatives.<sup>21</sup>



**Fig. 1.** A Schematic Illustration of Behavioral Sensitization. Each vertical arrow represents a psychosocial stressor, with the length of the arrow representing its “objective” severity. The stressor induces a certain response, which can be defined in terms of neurochemical (eg, striatal dopamine release, serum cortisol, or homovanillic acid elevation), behavioral (eg, locomotor reaction, cocaine self-administration in animal studies), or psychotic symptom alterations. As illustrated, the repeated exposure to severe psychosocial stress increases the behavioral, neurochemical, or psychometric responses to a later exposure of a new psychosocial stressor, even if this later exposure is not as severe as the previous one(s). This phenomenon is referred to as “behavioral sensitization” and is thought to play an important role in the way how psychosocial stress such as migration, discrimination, urbanicity, and childhood trauma may increase the risk for psychosis. The time intervals between these stressors can be weeks to months or even years, but for the sake of simplicity, the stressors directly follow each other in the above schematic illustration.

These findings suggest that the association between stress and psychosis may be a consequence of an underlying vulnerability, characterized by increased emotional and psychotic reactions to stress. Interestingly, increased stress reactivity was found to be unrelated (or even inversely related) to cognitive impairment, an intermediary phenotype associated with genetic risk for schizophrenia, thus suggesting the existence of different stress- and non-stress-related independent pathways to psychosis.<sup>22,23</sup> The stress reactivity pathway, which has also been termed the “affective pathway to psychosis,” has been hypothesized to preferentially underlie the positive symptoms of psychosis.<sup>20</sup>

### *Behavioral Sensitization to Stress*

In order to understand stress reactivity pathways, “sensitization” may be hypothesized to represent an underlying mechanism.<sup>24</sup> Sensitization refers to the process whereby (repeated) exposure to a certain event increases the behavioral and biological response to later exposure to a similar event, even if the later exposure is not as severe (schematically depicted in figure 1). Increased emotional and psychotic reactions to stress may be the result of such a process of behavioral sensitization, occurring when previous exposures to severe or enduring stressors

result in increased responses to the small stresses of daily life. Indeed, previous exposure to childhood trauma<sup>25</sup> or life events<sup>26</sup> has been suggested to increase the sensitivity to small stresses in daily life, the cumulative impact of which may lead to the development of impairment and need for care in individuals with initially subclinical or schizotypic levels of psychosis expression.<sup>20</sup>

### Biological Mechanisms Relating Stress to Psychosis

In order to understand sensitization and the possible genetic underpinnings thereof, it is important to have a plausible hypothesis of the biological mechanisms involved. The putative systems currently being explored are (1) the hypothalamus-pituitary-adrenal (HPA) axis because it mediates the principal adaptive response to perceived psychological or physiological stress and (2) the dopamine system, which is considered to be important in the development of psychosis.<sup>27</sup>

#### *HPA Dysregulation and Psychosis*

An enhanced response to stress mediated by activation of the HPA axis is thought to play an important role in the onset, exacerbation, and relapse of schizophrenia. A contribution by Walker and Diforio,<sup>28</sup> recently updated,<sup>29</sup> proposes a “neural diathesis-stress model,” suggesting that the HPA axis may trigger a cascade of events resulting in neural circuit dysfunction, including alterations in dopamine signaling. This model is based on evidence regarding effects induced by HPA axis hormones, especially cortisol, on brain and behavior. The authors conclude that several lines of evidence suggest a link between HPA activity and psychosis.<sup>28,29</sup> First, illnesses known to be associated with elevated cortisol (eg, Cushing syndrome) and the administration of corticosteroids have been observed to induce psychotic symptoms. Second, patients with schizophrenia and other psychotic disorders manifest HPA dysregulation, such as increased baseline cortisol and adrenocorticotrophic hormone levels,<sup>30–32</sup> increased cortisol response to a pharmacologic challenge,<sup>28,33</sup> and possibly also abnormalities in glucocorticoid receptors.<sup>34–36</sup> Furthermore, pronounced reductions in volume of the hippocampus have been described,<sup>37,38</sup> a brain region that plays a key role in dampening HPA activity. Hippocampal volume is in part genetically determined, but the environmental contribution to hippocampal volume is greater,<sup>39,40</sup> suggesting a potential role for HPA-mediated stress responses. Third, there may be a synergistic relation between activation of the HPA axis and activation of dopaminergic circuits that have been implicated in psychosis. Although the exact mechanisms remain to be elucidated, evidence suggests that glucocorticoid secretion may increase dopamine activity in certain brain regions,<sup>41–43</sup> in particular the mesolimbic system.<sup>44</sup> Fourth, factors implicated in the etiology of

schizophrenia, especially prenatal factors, can contribute to HPA dysregulation. These factors include prenatal exposure to maternal stress or glucocorticoid administration,<sup>45</sup> drugs of abuse, and various forms of pre- and perinatal complications.<sup>46</sup> For example, studies of the neurochemical effects of tetrahydrocannabinol, which is increasingly being recognized as a factor increasing the risk for psychosis,<sup>47</sup> indicate that it augments cortisol release in both nonclinical populations and individuals with schizophrenia.<sup>48,49</sup> Stimulants such as amphetamines, which are associated with increased risk for psychosis, also increase cortisol secretion in humans.<sup>50</sup> In contrast, the opiates appear to have little or no psychotogenic effect but rather depress cortisol secretion in humans.<sup>51</sup> A number of studies suggest that childhood abuse and neglect affect HPA axis functioning (for review see Tarullo and Gunnar<sup>52</sup> and De Bellis et al<sup>53</sup>). The evidence that childhood trauma constitutes a risk factor for psychosis remains controversial as discussed earlier,<sup>13</sup> but early, prolonged, and severe trauma may increase risk for later psychosis through lasting effects on the HPA axis.<sup>12,29</sup>

A recent meta-analysis<sup>54</sup> found that cortisol responses to stressor tasks associated with social-evaluative threats had an effect size of  $d = 0.67$ , compared with an effect size of  $d = 0.21$  for tasks without a social-evaluative component. These findings suggest that social-evaluative stressors and/or uncontrollability over them might be important in cortisol overactivity that may in turn mediate the effects of stress in triggering or worsening the symptoms of psychosis in those with a preexisting vulnerability.<sup>29,55</sup> The latter may be important because HPA dysregulation has also been implicated in other psychiatric disturbances, eg, affective disorders, suggesting that in individuals with a genetic vulnerability to depression, HPA dysregulation may compromise serotonergic system function and lead to depression, whereas among individuals who have an inherited liability to psychosis, elevated cortisol may induce or sustain psychotic symptoms through its impact on dopamine signaling.

#### *Dopamine and Psychosis*

It has been suggested that dopamine dysregulation may be implicated in the development of psychosis.<sup>27</sup> A sensitization process involving dopaminergic dysregulation of key brain areas has been proposed as the final common pathway leading to psychosis<sup>56</sup> and, indeed, as a potential model for schizophrenia including its cognitive and negative symptoms.<sup>57</sup>

Positron emission tomography studies have shown that drug-naïve schizophrenia patients display greater striatal dopamine release than controls when administered amphetamine.<sup>58</sup> Moreover, the degree of dopamine release following amphetamine administration may correlate with the severity of experimentally induced psychotic symptoms as well as with the response to

subsequent antipsychotic treatment.<sup>58–60</sup> Acute amphetamine administration can produce or enhance a psychotic reaction in patients with schizophrenia at doses that are usually ineffective in healthy individuals,<sup>61,62</sup> although this effect was not always found.<sup>63</sup> Individuals with schizotypal personality disorder also show a greater amphetamine-induced dopamine release than controls, albeit to a lesser degree than acutely ill schizophrenia patients.<sup>64</sup>

In addition to increased striatal dopamine release in psychosis, an interaction between striatal dopamine hyperactivity and frontal dopamine hypoactivity has been proposed, with frontal dopamine hypoactivity being associated with some of the neurocognitive deficits typically seen in schizophrenia.<sup>65</sup> This hypothesis is in agreement with the tonic-phasic dopamine theory introduced by Grace,<sup>66</sup> which differentiates between phasic and tonic dopamine release. Thus, low tonic activity in the prefrontal cortex is associated with negative symptoms and cognitive impairments; under conditions of cortical hypoactivity, the regulation of stressful stimuli is not optimally regulated by the frontal and temporal cortex, resulting in increased phasic dopamine release in the striatum. According to this model, striatal dopaminergic hyperactivity is conceived as a downstream effect of a reduced tonic dopaminergic activity in the prefrontal and temporal cortex.<sup>67</sup>

### Stress and Dopamine Reactivity

Dopamine dysregulation involving striatal dopamine sensitization may thus represent a common mechanism, linking multiple environmental exposures to a underlying biological mechanism of psychosis.<sup>24,56,68</sup> If this hypothesis is true, psychosocial stress should affect dopaminergic reactivity. The available literature relating stress to dopamine reactivity can be divided into 3 complementary approaches, ie, (1) animal studies, (2) studies using experimental metabolic stress models in humans, and (3) studies using true psychosocial stressors in humans.

#### *Animal Models of Stress-Induced Dopamine Reactivity*

Studies in rats have shown that dopamine release in response to an acute stressor is greater in the prefrontal cortex than in the striatum.<sup>69,70</sup> Furthermore, depletion of dopamine in the prefrontal cortex of rats enhanced the stress-evoked dopamine release in the shell of the nucleus accumbens.<sup>71</sup> It has thus been proposed that the stress-evoked increase in dopamine release in the prefrontal cortex in these rats attenuates the stress-evoked activity of dopamine neurons in the striatum in response to an acute stressor.<sup>72</sup>

Elaborating on the idea of sensitization, one study found that the presence of an acute novel stressor elicited an enhanced release of extracellular dopamine in the prefrontal cortex of rats previously exposed to chronic cold

stress for several weeks, but, remarkably, no such enhanced dopamine release was found in striatal structures in these chronically stressed animals.<sup>70</sup> This finding in chronically stressed rats seems to contradict findings in humans, which report a dose-response relationship between the number of traumas experienced and the risk for psychosis.<sup>5</sup> The results are also in contrast with a study in mice exposed to chronic social defeat stress:<sup>73</sup> chronic social defeat stress increased the firing rate of dopamine neurons in the ventral tegmental area, which subsequently gave rise to an increase in brain-derived neurotrophic factor (BDNF) signaling in the nucleus accumbens. These effects were not seen after a single episode of social defeat,<sup>73</sup> which seems compatible with the idea of behavioral sensitization following chronic social defeat stress as proposed by Selten and Cantor-Graae.<sup>14,15</sup>

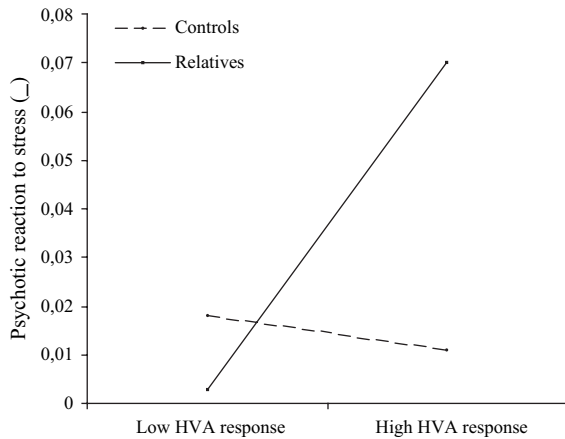
#### *Dopamine and Psychosis in Humans: Dopaminergic Reactivity to Metabolic Stress*

A second interesting paradigm to model the influence of stress on dopaminergic reactivity is the use of a metabolic stressor, such as intravenous infusion of 2-deoxy-D-glucose (2DG). This glucose analogue inhibits intracellular glucose metabolism and produces a mild, transient state of intracellular hypoglycemia.<sup>74</sup> This paradigm has been found to induce a robust activation of the HPA axis and also raises the plasma levels of homovanillic acid (HVA), a breakdown product of both dopamine and noradrenaline.<sup>75–77</sup> The effects of 2DG on the catecholamine and neuroendocrine systems can be assessed by repeatedly measuring HVA and cortisol in plasma over time.<sup>75</sup> In healthy controls, 2DG administration was found to evoke striatal dopamine release, which supports the use of the 2DG paradigm to study dopaminergic reactivity in psychosis.<sup>78</sup>

It has been consistently found that patients with schizophrenia display an increased HVA response to metabolic stress.<sup>75–77</sup> Furthermore, it has been found that unaffected siblings display an HVA response to metabolic stress at levels that are intermediate to those of their sibling-patients and controls,<sup>77,79</sup> an effect that was also found in any first-degree relative, although statistically inconclusive.<sup>76</sup> One study in first-degree relatives of patients with a psychotic illness and in healthy controls specifically assessed HVA reactivity to 2DG as well as reactivity to daily life stress using the ESM.<sup>80</sup> This study found that dopaminergic hyperresponsivity as measured by HVA reactivity to 2DG was associated with increased psychotic reactions to daily life stress in the first-degree relatives, whereas no such effect was found in the controls (figure 2).

#### *In Vivo Imaging Studies of Dopaminergic Reactivity to Psychosocial Stress in Humans*

Few studies have assessed in vivo dopaminergic reactivity following a true psychosocial stress task, probably



**Fig. 2.** First-Degree Relatives With High Homovanillic Acid (HVA) Response to the Metabolic Stressor 2-Deoxy-D-Glucose Display an Increased Psychotic Reaction to Small Stressors in the Flow of Daily Life, but No Such Response Was Found in First-Degree Relatives With Low HVA Response. This effect was not found in the healthy controls. Figure adapted from *Biol Psychiatry* 2005;58: 105–110.

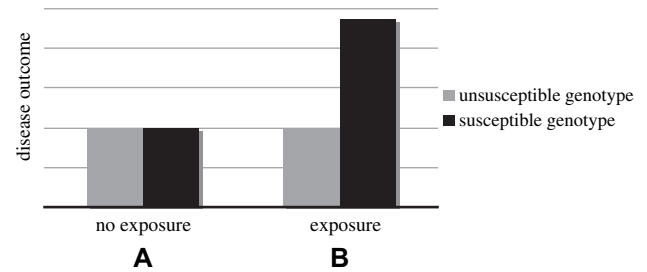
because of the complexity of combining a psychosocial stress task with imaging conditions. In 120 healthy college students, a psychosocial stress task was found to cause a significant release of dopamine in the ventral striatum.<sup>81</sup> Furthermore, individuals who had experienced low maternal care had increased striatal dopamine release in reaction to a social stress task compared with individuals with high maternal care, a finding suggestive of sensitization in this group.<sup>81</sup>

A recent study examining dopaminergic reactivity in the brain of individuals psychometrically at risk for psychosis found that a social stress task elicited an increased striatal dopamine release, more specifically in individuals with high levels of negative schizotypy but not in individuals with high levels of positive schizotypy, compared with control subjects.<sup>82</sup> Although increased dopamine release has commonly been found to be associated with positive symptoms, the genetic liability to schizophrenia may be better indexed by negative than positive symptom schizotypy.<sup>83</sup>

For example, scores of negative but not positive schizotypy were found to be increased in relatives of schizophrenic patients.<sup>84,85</sup> As such, high negative schizotypy scores may better capture the genetic risk for psychosis, which could explain why an increased stress-evoked dopamine release was only found in the group with high psychometric negative schizotypy.<sup>82</sup> However, many schizotypy instruments exist that may all display differential associations with genetic liability.

### Interaction Between Genetic Vulnerability and Environmental Stressors

So far, it has been argued that stress may be associated with psychosis by sensitizing persons, both at the behav-



**Fig. 3.** Illustration of a Typical Example of Gene-Environment Interaction. In situation A, there is no exposure to the environmental pathogen. In this situation, the risk for the disease outcome (eg, psychosis), as expressed on the y-axis, is similar for the low and the high susceptibility genotype. In situation B, there is additional exposure to the environmental pathogen. In the low susceptibility genotype, the risk for the disease outcome remains similar, whereas in the high susceptibility genotype there is an increase in risk.

ioral and the neurobiological level. However, individuals likely differ in their susceptibility to this sensitization process. A mechanism that could potentially explain between-subject differences is gene-environment interaction ( $G \times E$ ). Gene-environment interaction occurs when the effect of exposure to an environmental pathogen on health is conditional on a person's genotype or, conversely, when environmental experience moderates genetic effects on health<sup>86</sup> (figure 3).

### Multiplicative Interaction, Additive Interaction, and Biological Synergism

Discussion of the topic of gene-environment interaction requires differentiation between statistical and biological models of interaction. Most commonly, studies use statistical models to assess whether genes and environment multiply each other's effects, the so-called multiplicative models. In the case of statistical multiplicative interaction, the effect of genetic predisposition and environment in combination exceeds the product of their isolated effects at the population level. One of the problems with the multiplicative approach is that it requires the assumption that individuals who were exposed to both factors cannot have contracted the illness because of the effect of just one of these factors alone ("biological parallelism").<sup>87</sup> Therefore, it has been argued that interactions between putative causal risk factors may be better studied in terms of biological synergism and parallelism, which can be estimated from the additive statistical interaction as described by Darroch.<sup>87</sup> Biological synergism refers to the proportion of the population exposed to both genes and environment that developed the illness (eg, psychosis) specifically because of the combination of these exposures; parallelism refers to the proportion of the population exposed to both genes and environment that developed the disease because of either genes or environment.

### *Indirect Evidence for Gene-Stress Interaction in the Development of Psychosis*

Studies on the effect of urbanicity on psychosis outcomes have found that the effect of urbanicity was greatest in those with higher levels of familial liability for psychosis.<sup>6,8</sup> The authors did not find evidence for multiplicative interaction but did find evidence for biological synergism between genetic predisposition and urbanicity, with 60%–70%<sup>6</sup> and 20%–30%<sup>8</sup> of individuals who had been exposed to both factors developing schizophrenia because of their synergistic effects. These results are in line with a study in a sample of 3000 young adolescents from the Early Developmental Stages of Psychopathology study<sup>88</sup> that found that the risk-increasing effect of urbanicity was present only in individuals with preexisting psychometric liability in the form of subclinical psychosis-like symptoms, with significant evidence for biological synergism.<sup>89</sup> Tienari *et al.*<sup>90</sup> found that among children at genetic risk for schizophrenia, those adopted into dysfunctional families had higher than normal rates of schizophrenia, while those adopted into harmonious family environments had rates that were similar to the general population. The authors found evidence for both multiplicative interaction as well as for biological synergism. In a recent study in 49 individuals with schizophrenia or schizoaffective disorder and 34 controls, the degree to which stress induced increases in symptoms was prospectively studied over a 9-month period.<sup>18</sup> Trait reactivity was found to be higher in patients than in controls and was also found to be stable over time in patients (control subjects were not reassessed). The occurrence of objectively stressful life events during the month before the follow-up interview predicted significant increases in psychotic symptoms in those patients with high trait reactivity but not in those with low trait reactivity, providing evidence that genetically influenced traits (“trait reactivity”) and stressful life events additively interacted in the development of psychotic symptoms.

Altogether the available evidence seems to support the existence of gene-stress interactions by suggesting that (1) differences in preexisting liability to psychosis may interact with environmental stress (eg, urbanicity) to induce psychotic symptomatology,<sup>6,7,89</sup> (2) differences in psychosocial stress-related factors such as quality of upbringing may interact with genetic predisposition to psychosis in the development of psychosis in individuals at genetic risk,<sup>90</sup> and (3) in existing psychotic illness, initial trait reactivity predicts the subsequent response to stressful life events.<sup>18</sup> Although suggestive, these data do not, however, provide a direct link between specific genes and sensitivity to stress in the development of psychotic symptomatology.

### *Molecular Genetic Evidence for Gene-Stress Interaction in Psychosis: Candidate Genes*

Few studies have attempted to specifically assess a direct link between specific genes and sensitivity to stress in the

development of psychotic symptomatology. In this paragraph, the available data are summarized.

**Catechol-O-Methyltransferase.** An obvious candidate gene that may be useful to investigate the genetic underpinnings of stress sensitivity is the catechol-O-methyltransferase (COMT) gene because it encodes an enzyme that is critical in the breakdown of dopamine, particularly in the prefrontal cortex. COMT contains a functional polymorphism that results in a change from valine (Val) to methionine (Met) (COMT Val158-Met) that directly affects enzyme function: individuals with the Val/Val genotype have a 40% higher brain COMT enzyme activity than individuals with the Met/Met genotype.<sup>91</sup>

It has been hypothesized that the effect of the Met allele would be to increase tonic dopamine and decrease phasic dopamine release subcortically and increase dopamine concentrations in the cortex, which would enhance tonic dopamine activity and D1 stimulation cortically. In contrast, the Val allele was hypothesized to increase phasic dopamine transmission while decreasing tonic dopamine neurotransmission subcortically and decreasing overall dopamine concentrations in the prefrontal cortex, thus reducing cortical D1 neurotransmission.<sup>92</sup> In partial support of this hypothesis, a recent study indeed suggested a lower dopaminergic tone in the cortex of healthy individuals with the Val/Val genotype compared with those with the Val/Met or Met/Met genotype as measured by [<sup>11</sup>C]NNC 112 binding, although no differences were found in the striatum.<sup>93</sup>

Three studies so far have examined a possible role of COMT Val158Met in stress-induced psychotic reactions. A study in 306 men between 19 and 24 years old entering compulsory military training found a significant additive interaction between COMT Val158Met and the stress associated with entering the military, with carriers of the Val allele showing the greatest increases in the Symptom Checklist-90—Revised items “paranoid ideation” and “psychoticism.”<sup>94</sup> A study in a general population twin sample found evidence for additive interaction between COMT Val158Met genotype and stressful events in a model of the ESM item “I feel suspicious” (C. J. Simons MSc, M. Wichers MA PhD, I. Myin-Germeys MA PhD, L. Krabbendam MA PhD, J. Van Os MD PhD, unpublished data). Again, individuals with the Val/Val genotype showed the largest increases in paranoia in response to these stressors. Thus, the above findings may add evidence to the hypothesis that a hypodopaminergic prefrontal state, which has been shown to be associated with the Val/Val genotype,<sup>93</sup> may facilitate the onset of stress-induced psychotic experiences at the level of the general population.

However, these results are in contrast with an ESM study in 31 cannabis-using psychosis patients and 25 healthy cannabis users that also suggested an additive interaction



between stressful events and COMT Val158Met genotype, but here the Met/Met patients showed the largest increases in psychotic symptoms as well as negative affect, whereas no interaction was found in the healthy cannabis users.<sup>95</sup> In turn, these findings are in agreement with general population studies that suggest that Met carriers may be less resilient to negative affective states such as pain,<sup>96</sup> react more strongly to experimentally induced metabolic<sup>97</sup> or psychosocial stress,<sup>98,99</sup> and tend to have an increased propensity to anxiety,<sup>100–103</sup> reduced extraversion,<sup>102,104</sup> and reduced novelty seeking.<sup>104–106</sup> Further studies, especially in at-risk populations, are needed to resolve these apparently contrasting findings with regard to a possible role of the COMT Val158Met polymorphism in stress-induced vulnerability to psychosis; interactions with other single-nucleotide polymorphisms (SNPs) up- or downstream may be one possible factor to explain divergent results, suggesting the use of haplotypes to model  $G \times E$  rather than single SNPs.

**Brain-Derived Neurotrophic Factor.** BDNF is a neurotrophin, a family of dimeric polypeptides that promote the growth and differentiation of developing neurons in central and peripheral nervous systems as well as survival of neuronal cells in response to stress.<sup>107</sup> Animal studies have shown that early adversities can influence BDNF expression and produce long-lasting effects on neurotrophic processes, thus impacting on neuronal maturation and plasticity in later life.<sup>108</sup> However, the results of studies investigating postmortem or plasma BDNF levels in patients with schizophrenia have been mixed (for review, see Buckley et al<sup>108</sup>).

A common Val/Met SNP at position 66 in the BDNF gene was recently identified as a functional polymorphism. The Val variant is associated with higher neuronal BDNF secretory activity than the Met variant.<sup>109</sup> In addition, the coexpression of Val and Met (in heterozygotes) results in less efficient intracellular trafficking and processing leading to decreased BDNF secretion. A recent study found that depression in children was predicted by a 3-way additive interaction between childhood adversity and BDNF and serotonin transporter (5-HTTLPR) polymorphisms: children with the Met allele of the BDNF gene and 2 short alleles of 5-HTTLPR had the highest depression scores but the vulnerability associated with these 2 genotypes was only evident in the maltreated children.<sup>110</sup> These findings were supported by another study in healthy female twins, although a main effect of BDNF Met on childhood adversity was also observed, possibly indicating confounding by gene-environment correlation.<sup>111</sup>

One study to date investigated a possible moderation by BDNF Val66Met of stress-psychosis associations. Simons et al examined a general population twin sample and modeled COMT-stress interactions using ESM as described earlier (C. J. Simons MA, M. Wichers MA PhD,

I. Myin-Germeys MA PhD, L. Krabbendam MA PhD, J. Van Os MA PhD, unpublished data). The authors reported evidence for additive interaction between BDNF Val66Met and stress experienced when being in social situations with company that participants disliked (“social stress”). As expected, BDNF Met carriers showed more social stress-induced paranoia than Val/Val carriers. To the best of our knowledge, no study to date has investigated possible similar moderation by functional variation in the serotonin transporter, despite evidence pointing to possible higher order interactions between variation in this gene and BDNF Val66Met<sup>110,111</sup> as well as COMT Val158Met<sup>112</sup> in models affective disorder.

**Genes Relating to the HPA Axis.** Most recognized risk factors for psychosis may involve activation if not chronic dysregulation of the HPA axis. From this perspective, HPA axis genes could be plausible candidates with respect to altering susceptibility to psychosis. To the best of our knowledge, however, no studies have as yet investigated possible gene-environment interaction between HPA axis-related genes and psychosocial stress in the development of psychosis. Nevertheless, HPA-related genes  $\times$  child abuse additive interaction in the expression of adult depressive and posttraumatic stress disorder symptomatology is emerging from the recent literature.<sup>113,114</sup> In these recent studies, genes involved in HPA axis regulation (polymorphisms within the CRHR1 and FKBP5 genes) moderated the effect of child abuse or trauma on the risk for developing adult psychopathology. Alternatively, resilience to genetically determined HPA overactivation may be involved, centrally or peripherally, in the etiological cascade of events that decreases risk for a number of psychiatric phenotypes including psychosis. Genes coding for subunits of the Gamma-aminobutyric acid type A (GABA-A) receptor that may influence cortisol and autonomic responses to psychological stress<sup>114</sup> may thus also be targeted because disturbances in the GABA-mediated system have been well documented in patients with schizophrenia and because the GABAA6 isoform is located on chromosome 5q34, a region found to meet criteria for significant genome-wide association with schizophrenia in a meta-analysis of 20 genome-wide scans.<sup>115</sup> Variants of the glucocorticoid receptor itself (NR3C1) have been associated recently with susceptibility to major depression,<sup>116,117</sup> but potential association with the psychosis phenotype has yet to be explored. Unknown also is whether genetic variation in stress-induced anxiolytic peptides such as neuropeptide 1, which explain interindividual variation in resilience to stress,<sup>118</sup> may also moderate environmental effects on psychosis risk. In a rare example of gene pleiotropy in psychiatry, variants of plexin A2 (PLXNA2) situated on chromosome 1q32, a possible candidate region for schizophrenia, have recently been associated independently within

a whole-genome association study with susceptibility to schizophrenia,<sup>119</sup> anxiety, and psychological distress.<sup>120</sup> A somewhat similar finding is that variants of the GPM6A gene, which moderates the influence of stress on the hippocampus in animals, were associated with a depression subtype of schizophrenia, suggesting that GMP6A plays a role in the stress-induced hippocampal alterations that are found in psychiatric disorders in general and schizophrenia in particular.<sup>121</sup>

**Concerns for  $G \times E$  Research.** The findings discussed in this review article suggest that studying gene-stress interactions can contribute substantially to our understanding of the pathogenesis of psychosis. Nevertheless, there also are a number of concerns. These include adequate sample size, the need for a hypothesis-driven approach, caution with regard to “pseudoreplications” (eg, an interaction effect only present in a certain subsample instead of in the whole sample or evidence for a 3-way interaction where originally a 2-way interaction was reported), use of appropriate statistical models including risk of multiple testing and models that can approach biological rather than statistical interaction, the appropriate choice of outcome measures, possible confounding by gene-stress correlation, and the reliable measurement of environmental factors (for details see Van Os and Poulton elsewhere in this issue).<sup>122</sup>

## Conclusions

Accumulating evidence suggests that psychosocial stress may be associated with an increased risk for developing psychosis. The evidence suggests that the association is particularly evident in case of cumulative exposure, an idea that is compatible with the concept of “behavioral sensitization.” The neurobiological substrate of behavioral sensitization may involve dysregulation of the HPA axis, contributing to a hypothesized final common pathway of sensitized dopaminergic projections. Sensitization of dopamine projections may result in increased striatal dopamine release in response to stress. Some evidence suggests that striatal hyperactivity may be influenced by the degree of tonic dopaminergic activity in the prefrontal and temporal cortex. Although few studies have specifically examined prefrontal-striatal dopamine balance in response to stress, and controversial findings have been reported, it may provide an elegant framework for developing and testing more specific hypotheses on dopaminergic reactions to stress in key brain areas.

Gene-environment interaction may be an important variable in explaining between-subject differences in the risk to develop psychosis following exposure to psychosocial stress. Nevertheless, studies investigating interactions between specific genetic variants and stressors are still relatively scarce, and their results have not always been consistent. Preliminary evidence suggests that poly-

morphic variation within the COMT and the BDNF gene may interact with psychosocial stress in the development of psychosis, yet further exploration of these and other candidate polymorphisms is urgently required.

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